# Study on the Etiology, Pathogenesis and Clinical Symptoms of Hashimoto's Thyroiditis

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**Abstract:** Hashimoto's thyroiditis (HT) is a common thyroid autoimmune disease with multiple impacts on the thyroid of patients. The main clinical manifestations include disorder of humoral and cellular immunity, and morphological and functional changes in the thyroid. There have been a variety of factors influencing the development of HT, such as genes, environment, uneven nutrition intake, and so on. The pathogenesis is complex and there is no method to completely cure and reverse HT. However, the exact etiology and pathogenesis have not been fully clarified. Therefore, the current research task is to understand the clinical manifestations, explore the pathogenic factors and study the pathogenesis. This article briefly introduces the main clinical features of HT and summarizes the research results of different scholars on the pathogenic factors and pathogenesis.

## 1. Introduction

Autoimmune thyroid disease (AITD) is an organ-specific autoimmune disease with high morbidity. There are about 5 cases per 100 people who suffer AITD worldwide[1]. Hashimoto's thyroiditis (HT), one of the most common types of AITD, was first reported in 1912 by Hashimoto. HT is known as chronic lymphocytic thyroiditis or autoimmune thyroiditis and is characterized by thyroid-specific autoantibodies, including thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibody (TG-Ab) [2, 3]. The clinical features of HT are composed of thyroid follicular cells destruction, chronic lymphocyte infiltration, elevated titers of TPO-Ab and TG-Ab, and painless thyroiditis. The dysfunction of the thyroid gland may lead to hypothyroidism or hyperthyroidism with the development of the disease [3, 4]. However, the exact etiology and effective methods for the prevention and treatment of HT are still unclear, which makes it impossible to achieve a radical cure. Therefore, exploring methods to prevent and treat HT based on the pathogenesis and pathogenesis is urgently needed for future research in HT[3]. Herein, we review the clinical manifestations of HT and summarize the current research status of HT, to provide references for the diagnosis, prevention, treatment, and drug development of HT in the future.

## 2. Clinical manifestations of HT

The clinical manifestations of HT may be mild at first and the disease progresses slowly[5]. In the early stage of HT, there were no obvious symptoms except the abnormal increase of TPO-Ab and TG-Ab levels in serum[6]. Although the symptoms of HT take years to develop, HT patients have certain changes in multiple aspects, including morphology, immune environment, behavior, and so on (figure 1).

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| The Clinical manifestations of HT | | |
|---|---|---|
| Morphological changes | Ultrasonic manifestations | thyroid gland enlargement |
| | | Inflammatory cell infiltration parenchyma |
| | | fibrous hyperplasia |
| | | calcification |
| | | vascular hyperplasia |
| | | thyroid hypoechoic |
| | | pseudo nodular |
| | | uneven parenchyma |
| Changes in Immune environment | Humoral immunity disorder | TG-Ab increase |
| | | TPO-Ab increase |
| | Cellular immune disorder | Th activate and proliferate |
| | | Th1 / Th2 ratio increase |
| Changes in thyroid function[8] | Hyperthyroidism, also known as Hashimoto's hyperthyroidism | |
| | subclinical hypothyroidism | |
| | Hypothyroidism | |
| | normal thyroid function with thyroid antibody | |

**Figure 1.** HT patients have certain changes in multiple aspects

## 2.1. Morphological changes in the thyroid

For diagnosis and evaluation of HT, ultrasound, an important non-invasive tool, is a reliable method to confirm the diagnosis and curative effect. The ultrasonic characteristics of HT include thyroid enlargement, inflammatory cell infiltration into the parenchyma, fibrous hyperplasia, calcification, and vascular hyperplasia. These changes result from abnormal antibodies or immune cells. In addition, HT patients also have thyroid hypoechoic, pseudo nodular, and uneven parenchyma[7].

## 2.2. Functional changes in thyroid

The thyroid function in HT patients has various manifestations, mainly including the following types: (1) Hyperthyroidism, also known as Hashimoto's hyperthyroidism; (2) subclinical hypothyroidism (serum thyroid-stimulating hormone [TSH] level increases, but serum free thyroxine [T4] and free triiodothyronine [T3] levels are normal); (3) Hypothyroidism (high TSH level, low T4, and T3 serum level); (4) Thyroid antibody exists but thyroid function is normal[8].

## 2.3. Immune Environment Changes

### *2.3.1 Disorder of humoral immunity.*

The main feature of HT is the presence of thyroid autoantibodies against two main thyroid antigens: TPO-Ab and Tg-Ab. They exist in more than 90% and 80% of HT patients, respectively. Therefore, one of the clinical detection methods of HT is to detect the circulating concentration of TPO-Ab and Tg-Ab in patients' serum. It is also the most convenient and commonly used method at present[2, 9].

### *2.3.2 Cellular immune disorder.*

The cells were activated and proliferated in HT patients. A mixed mRNA pattern of cytokine secretion revealed that Th1 and Th2 subtypes of helper T cell response are related to HT. HT is caused by the cellular immune mechanism mediated by Th1. The Th1/Th2 ratio of HT patients is higher than that of healthy ones. In Th1 cells of HT patients, lymphocytes activate a strong thyroid lymphocyte inflammatory infiltrate, resulting in subsequent thyroiditis and thyroid damage[10].

## 2.4. Emotion changes

As mentioned above, HT patients can be roughly divided into three groups: hyperthyroidism, hypothyroidism, and normal thyroid function. It has been proved that HT patients with normal thyroid function have a higher degree of anxiety and depression[11]. Hyperthyroidism can be accompanied by emotional problems, which has been proved by animal experiments and patient follow-up experiments[12, 13]. HT patients with hyperthyroidism also have more negative emotions. As for HT patients with hypothyroidism, there are also many studies proving that they have more anxiety and depression than healthy people[11]. Therefore, negative emotions are a symptom

of HT patients and have nothing to do with whether thyroid function is normal.

## 3. Pathogenic factors of HT

### 3.1. Genetic factors

There are several genes related to HT. The first gene associated with AITD was found to be Human leukocyte antigen (HLA). In normal thyroid follicular epithelial cells, the level of HLA antigens is low. However, according to reports, high levels of HLA antigens have been detected in HT patients, indicating that the HLA gene plays a major role in the pathogenesis of HT. Another related gene is cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). It is a negative regulator and expressed in activated T lymphocytes. Studies showed that the polymorphism of the CTLA-4 gene is closely related to the susceptibility to HT [14, 15]. In addition, Tg is a thyroid-specific AITD susceptibility gene and a target of autoimmune reaction: TG Ab is a marker antibody of HT [16].

However, the relationship between genetic genes and HT is complex, and there are differences among different ethnic groups and regions. Even if multivariate models are applied, the risk of HT cannot be predicted. Therefore, the association of individual genes with HT should be interpreted very carefully [17].

### 3.2. Excessive iodine intake

Iodine is one of the raw materials for thyroxine synthesis. Excessive iodine intake can lead to thyroid dysfunction, including HT[18]. Excess iodine intake, or the increases of iodine intake of iodine deficient people after iodine fortification, gives an increased risk of HT. In China, three years after salt iodization began in 1996, the prevalence of AITD was 0.5% in regions with mild iodine deficiency, 1.7% in regions with insufficient iodine intake, and 2.8% in regions with excessive iodine intake[19].

### 3.3. Selenium deficiency

Studies have reported that selenium has a large part to play in the thyroid. Selenium is mainly used to synthesize three thyroxine deiodinases, catalyze reduced glutathione converting into oxidized glutathione, turn toxic peroxides into non-toxic hydroxylates, reduce the damage of free radicals to the thyroid, and assist in maintaining the steady state of thyroid hormone metabolism. Low serum selenium levels can cause immune disorder and chronic inflammation of thyroid tissue[20]. Clinical research has shown that selenium supplementation treatment can reduce the level of autoantibodies, inhibit the increase of antibodies and the further deterioration of thyroid tissue, and improve the immune function of patients with HT[18].

### 3.4. Vitamin D deficiency

Vitamin D is a regulator of the immune system. Its deficiency directly affects the level of thyroid autoantibodies and the progress of HT. After supplementing with vitamin D, the serum levels of TG-Ab and TPO-Ab were decreased notable in HT patients, which resulted in to reduction in the probability of hypothyroidism [20].

### 3.5. Environment

Studies are showing that breathing polluted air may cause AITD, but the pathophysiological mechanism is still unclear. A view is that smoking can trigger autoimmune diseases[4]. However, a cross-sectional study found that smoking was associated with the significant decrease of TSH, TPO-Ab, and TG-Ab levels, which indicated that smoking played a delaying role in HT's development . Therefore, there is no reasonable explanation for the fact that smoking works as a pathogenic factor or a delaying role in the process of HT development. In the case of thyroid autoimmunity, environmental factors can aggravate the degree of autoimmune reaction and accelerate the process of disease.

### 3.6. Infection

After the body is infected by bacteria or viruses, the expression of self-antigens increases, inducing abnormal expression of MHC antigens, which will break the balance of the immune system and probably lead to the occurrence of HT. Both hepatitis C virus and human herpesvirus 6 may have a molecular mimetic mechanism with their antigens, causing the deterioration of HT. Helicobacter pylori infection is also closely related to HT's occurrence and development .

### 3.7. Emotion

Stress is considered one of the factors that directly and indirectly affect the immune system through the nervous and endocrine systems respectively. Some studies found that in HT patients, there is a positive correlation between somatic anxiety and thyroid autoantibody status. Anxiety experienced at a somatic level can induce immune modulations, then further lead to or aggravate autoimmune diseases, especially in genetically susceptible individuals. Additionally, the depression and anxiety disorder scores of HT patients were remarkable higher than those of healthy controls, as demonstrated in a recent meta-analysis of 19 studies with 36174 participants . It indicates that patients with depression and anxiety should be screened for HT so as not to delay their condition.

### 3.8. Obesity

Meta-analysis shows that the probability of thyroid autoimmunity in obese people is increased. There was a relevance between TPO-Ab positive and obesity: obesity is bound up with an increased risk of TPO-Ab positive by 93%. Adipokines may play a vital role in immune disorders. Leptin is one of the adipokines, which is believed to regulate the immune system and help to increase the production of TPO-Ab.

### 3.9. Medicine

Drugs regulating the immune system may induce HT. It has been shown that thyroid cells exposed to Interferon-α (IFN-α) in vitro increased the release of pathogenic thyroglobulin peptide in vivo. Immune checkpoint inhibitors can remove the brakes on T cell activation, have harmful side effects: lead to autoimmune diseases, and may cause hypothyroidism. In addition, the use of IFN-α may induce HT, and tyrosine kinase inhibitors are also related to the pathogenesis of HT.

### 3.10. Intestinal flora

The thyroid and intestine have a common embryonic origin. Many studies have shown that the thyroid-gut axis has both advantages and disadvantages on thyroid function. Intestinal microbes regulate the secretion of thyroid hormones, thereby changing thyroid function. The meta-analysis shows that the intestinal flora of HT patients is dysregulated and more abundant. This may be caused by the overgrowth of intestinal bacteria, while the proportion of beneficial bacteria (e.g. Lactobacillus and Bifidobacterium) is significantly reduced. Some intestinal flora showed a significant correlation with TPO-Ab. Similarly, the increase of antibody and thyroid hormone levels in HT patients may affect and change the composition and number of intestinal floras. However, it is still unknown whether intestinal microbes affect the specific mechanism of triggering HT and how to regulate autoimmunity in HT patients. In addition, probiotics have a good effect on thyroid diseases and can be used as an auxiliary treatment for thyroid diseases. However, most probiotics studies rely on animal models. That means well-designed human studies are needed to further clarify the importance of the thyroid gut axis and the possibility of intervention.

### 3.11. Epigenetics

The current study shows that genetic and environmental factors synergistically determine HT by regulating epigenetic factors. There are many epigenetic factors related to HT, such as methylation, histone modification, and epigenetic modification by RNA interference of non-coding RNA, which further increase the occurrence of HT in genetically susceptible individuals. Evidence suggests that the predominance of women in HT may be due to X chromosome inactivation, which is considered a major epigenetic feature.

## 4. Pathogenesis

As an autoimmune disease, the pathogenesis of HT is complex and connected with multiple kinds of factors, including T lymphocyte, oxidative stress, apoptosis, and so on.

### 4.1. Imbalance of T lymphocyte subsets and related cytokines

Tlymphocytes and the relative cytokines play an essential role in the occurrence of HT. Under the stimulation of different cytokines, Naïve CD4+T cells (Th0) differentiate into many effector subsets, including T helper 1 (Th1), Th2, Th17 and regulatory T cell (Treg). An imbalance of the cell ratio of Th1/Th2 and Th17/Treg can cause immune dysfunction, leading to the occurrence of AITD (Figure 2).

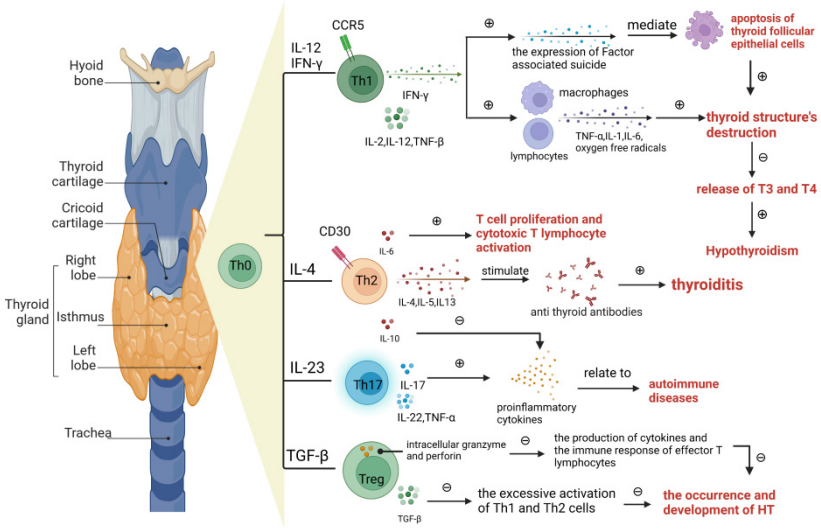


**Figure 2.** Development of CD4 T cells and functional diversity of CD4 subsets in HT.

Naïve conventional T cells (Th0) in thyroid tissue are regulated by antigens, cytokines, and other factors, then differentiate into different types of Th cell subsets to mediate different kinds of immune response. The imbalance of T cell subsets and their cytokines damages the immune homeostasis and leads to thyroid autoimmunity. Some cytokines could cause HT. High levels of IFN-γ increase apoptosis-associated factors (Fas) expression and mediates apoptosis of thyroid follicular epithelial cells. interleukin (IL)-10 and IL-17 affect immune homeostasis by regulating the level of inflammatory factors related to autoimmune diseases.

Some cytokines could inhibit inflammatory reactions and maintain immune homeostasis to postpone the development of HT. Intracellular granzyme and perforin inhibit cytokine production. transforming growth factor (TGF)-β inhibits the overactivation of Th1 and Th2 cells. Both of them play a slowing and inhibiting role in the occurrence and development of HT. In the figure, ⊕ represents promotion; ⊖ represents inhibition.

In HT patients, excessive Th1 cells and high levels of inflammatory cytokines (e.g. interferon (IFN)-γ) were found. Th1 cells secrete many cytokines (e.g. interleukin (IL)-1α, IL-2, IL-1β, IFN-γ, tumor necrosis factor (TNF)-α, and TNF-β) and these can trigger the activation of CD8+cytotoxic cells, leading to thyroid cells destruction, eventually gland atrophy and hypothyroidism. The classical characterization of HT is that lymphocyte infiltrate and destruct thyroid follicular cells, in which IFN-γ is critical. The IFN-γ expresses increasingly in the development of HT. IFN-γ upregulates the expression of Fas to mediate thyroid follicular epithelial cells' apoptosis, resulting in serious thyroid structure destruction and thyroid dysfunction. Moreover, it can promote lymphocytes infiltrating in the thyroid or inducing macrophage activation and lymphocyte infiltration; these cells release cytokines (e.g. TNF-γ, IL-1, IL-6, and oxygen radicals) to cause thyroid tissue damage. The damaged thyroid would suppress the release of T3 and T4, leading to hypothyroidism[10].

Nodehi, M., et al. reported that excessive Th2 cells exist in HT patients, indicating that Th2 cells are related to HT. Th2 cells secrete specific interleukins (e.g. IL-13, IL-10, IL-4, IL-5, and IL-6), stimulate the anti-thyroid antibodies' production and promoting the thyroiditis' development. IL-6, a typical pro-inflammatory cytokine, is highly expressed in HT and can promote T cell proliferation and cytotoxic T lymphocyte activation. However, IL-10 can inhibit the immune response by downregulating proinflammatory factors. In HT patients, IL-10 express in the event of immune imbalance, which may be the self-protection mechanism of the body.

In HT patients, IFN-γ is highly expressed while IL-4 is contrary, indicating that Th1 cells that secrete IFN-γ are the main Th cells infiltrating in HT thyroid tissue, and due to the predominance of Th1 cells, imbalance of Th1/Th2 cell occurs and causes abnormal immune responses and diseases of the thyroid. It can be considered that the increased Th1/Th2 ratio is one of the causes of HT.

Another type of T cell subpopulation is Th17 cells, whose discovery supplements the deficiency of Th1/Th2 cell immune regulation theory. Th17 cells primarily secrete IL-17 and IL-22. In HT patients, Th17 cells' number and the level of IL-17 increased significantly, which was positively correlated with TPO-Ab. High levels of IL-17 can cause inflammation and tissue damage, and promote the occurrence of AITD.

Treg cells and their cytokines are important reference indicators for the study of autoimmune thyroiditis, playing an immunosuppressive role in HT's occurrence and development. The results of an experiment showed that Tregs' percentage was significantly decreased and inverse correlation to thyroid function states in HT patients. Treg cells inhibit the immune response in two ways: one is to inhibit the production of cytokines and the immune response of T lymphocytes through intracellular granzyme and perforin; the other is to secrete TGF-β to maintain peripheral immune tolerance, which could prevent Th1 and Th2 cells over-activation.

Tlymphocyte subsets and their special cytokines play an essential role in the process of regulating the immune response. They are mutually regulated and restricted. For instance, Th2 cells inhibit Th1 and Th17 cells' differentiation. IL-12 and INF-γ can promote the differentiation of Th1 and inhibit the proliferation of Th2, while IL-4 and IL-10 promote the differentiation of Th2 and inhibit the proliferation of Th1. The abnormal expression of these T lymphocyte subsets and cytokines will cause immune dysfunction, lead to abnormal immune responses, and participate in HT's occurrence and development.

### 4.2. Apoptosis

In normal thyroid tissues, death receptors and their ligands are inactive, such as apoptosis-associated factors (Fas) and its ligand (FasL). However, during inflammation, the activations of pro-apoptotic molecules are enhanced while the expression of anti-apoptotic molecules is reduced. Apoptosis is the process that removing unnecessary cells and the cells with pathological changes to better maintain the stability of the internal environment. However, abnormal apoptosis may lead to failure to clear autoreactive lymphocytes, thus leading to autoimmune diseases' occurrence and development .

Fas and FasL are membrane surface factors related to cell apoptosis. Fas is involved in the clearance of autoreactive lymphocyte clones in peripheral lymphoid organs, and the overactivated T cells caused by foreign antigens. Unlike the widely distributed Fas, FasL usually only appears in activated T cells (especially cytotoxic T cells) and natural killer (NK) cells, while other cells (e.g. B cells and fibroblasts) do not express this ligand. So, it is considered to be an important way to cause apoptosis of thyroid cells in AITD patients. Studies have shown that infiltrating lymphocytes do not directly participate in the killing of thyroid cells by their own FasL. Instead, they generate cytokines to stimulate the autocrine or paracrine action of thyroid follicular cells. They act on their cells and adjacent activated T cells and carry out autocrine killing and paracrine killing respectively, leading to cell death.

B-cell lymphoma 2 (Bcl-2) is an anti-apoptotic molecule. Myeloid cell leukemia-1 (MCL-1) is the main protein associated with BCL-2. It exists in the outer mitochondrial membrane and related to the survival of lymphocytes. The evaluation of anti-apoptotic markers' expression in lymphocyte infiltration indicated that BCL-2 and MCL-1 were expressed more frequently in HT patients than in healthy people. It indicates that anti-apoptotic and proapoptotic forces were constantly seeking balance in the inflammatory state of AITD. But as early as 1996, studies showed that Bcl-2 in HT patients was down-regulated in the early event leading to programmed cell

death. It may be directly caused by lymphocyte-derived cytokines or by activated functional Fas pathway before cell apoptosis.

Caspase, a proteolytic enzyme closely related to apoptosis, also plays a vital role in thyroid follicular epithelial cells apoptosis. In the apoptosis process, the Bcl-2 family and the death agonist (Bid) in the interaction domain of apoptosis-promoting protein BH3 can activate caspase-8 molecules. Then they initiate endogenous pathways to activate apoptosis and release cytochrome C. In the presence of dATP, the cytochrome C released into the cytoplasm combines with apoptosis-related factor 1 (APAF-1), and promotes the combination with caspase-9 to form apoptotic bodies. Activated caspase-9 can also activate caspase-3 and other caspases to induce apoptosis. Some studies have shown that HT patients mainly express apoptotic markers, such as Bid and Fas, near lymphocyte infiltration. So, they are more likely to produce cytotoxicity.

### 4.3. Oxidative stress (OS)

OS refers to the imbalance between oxidation and antioxidation in the body. It leads to neutrophils' inflammatory infiltration and increased protease secretion. It also destroys the balance of oxidants and antioxidants in the body, resulting in cell damage. Excessive OS will promote inflammation and apoptosis, impair immune tolerance, and then further cause the occurrence of various autoimmune diseases. Under normal circumstances, the thyroid itself has a complete antioxidant enzyme system. It can form an antioxidant barrier to prevent the thyroid from being damaged by superoxide free radicals. Although the oxidation environment is generated when synthesizing thyroid hormones, the redox balance can be properly controlled without affecting normal function. It is demonstrated that many factors may induce the OS of HT. In thyroid cells, Th1 cytokines can induce the increase of NADPH oxidase (NOX4). NOX4 not only produces H2O2 and superoxide but also reduces antioxidant proteins (e.g., peroxiredoxin 1 (PRDX1), catalase (CAT), and superoxide dismutase 1 (SOD1)), thus causing OS. Also, an imbalanced diet and undernutrition result in insufficient intake of some trace elements such as copper, selenium, manganese, and iron. It can affect the production of antioxidant enzymes and destroy the redox level as well. What's more, with the growth of age, the thymus degenerates and leads to the decrease of the renewal of naive T cell population and peripheral T cell types. The opportunity for autoimmune diseases and DNA damage caused by OS then increases.

### 4.4. miRNA

miRNA is a small endogenous non-coding RNA molecule. It can regulate the differentiation of immune cells, signal transduction, immune response, and other aspects. Finally, it can regulate the immune response mildly and finely by doing these. Domestic scholars found that several miRNAs (miR-205, miR-296, miR-20a-3p, miR-375, and miR-451) were significantly up-regulated in the plasma of HT patients. The overexpression of miR-296 in HT has a potential negative impact on the growth of thyroid cells, which may be related to hypothyroidism. The ectopic expression of miR-451 reduces cell viability, accelerates cell death, and promotes cell apoptosis in a caspase-3-dependent manner. It may promote the development of HT in this way. However, some studies have shown that the high expression of miR-375 in plasma is negatively correlated with TSH level, and the high expression of miR-20a-3p is negatively correlated with TgAb level. These are inconsistent with the clinical manifestations of HT. The relationship between the high expression of miR-375, miR-20a-3p, and HT needs further study.

### 4.5. NK cells

NK cells are the third type of lymphocytes different from T and B lymphocytes, which play both positive and reverse regulatory and induction roles in the development of AITD. On the one hand, NK cells can secrete a variety of cytokines, inhibit or even destroy T and B lymphocytes, and inhibit autoimmune diseases. On the other hand, it may interfere with antigen-presenting cells (APC), stimulate autoreactive T lymphocytes and B lymphocytes, and promote the occurrence of autoimmune diseases. Therefore, the role of NK cells in HT's occurrence and development is often controversial. It has been mentioned that in some studies on the difference in NK cell activity between HT patients and healthy people and the correlation between NK cell activity and anti-thyroid antibodies, some results showed that there were differences and correlations, and some did not. This could not accurately explain the correlation between NK cells and HT. However, the increase of NK cell levels in female HT patients is positively correlated with recurrent spontaneous abortion. This finding indicates that compared with healthy people, the NK cell immune status in HT patients is abnormal. The inhibition of NK cell activity means the potential expansion of T/B cell function. It leads to the up-regulation of autoreactive T lymphocytes, the production of thyroid-specific autoantibodies, and the migration and infiltration of lymphocytes into the thyroid. Therefore, the change in NK cell activity can promote the HT's occurrence and development.

### 4.6. Antibodies and Antigens

The two main antigens of autoimmune thyroiditis are TG and TPO [3]. The level of thyroid autoantibodies remains constant under normal physiological conditions, but it increases in the event of disease. Studies have shown that the increase of this kind of antibody level is positively related to the symptoms of HT, which reflects the degree of thyroid autoimmunity to a certain extent. The elevated TPO-Ab and TG-Ab titers will cause lymphocyte infiltration and lead to thyroid destruction [3].

There are also reports of antibodies that bind to thyrotropin receptors and block their action, which may play a role in further damage of thyroid function. Other antigens also play a role in the HT's occurrence and development, Menconi et al. believe that human Tg.2098

is the main human T cell antigen, which leads to HT by initiating autoimmunity. There are other proteins relating to thyroid function, such as sodium iodide transporter (NIS). It is a key protein in normal thyroid cell physiology, responsible for the active transport of iodine on the basal lateral membrane of thyroid cells. It also plays a key role in maintaining normal thyroid cell function and proliferation. Many patients with AITD have the phenomenon of NIS overexpression. At present, whether NIS is the autoantigen of HT is still under discussion.

## 5. Conclusions and perspectives

HT is an organ-specific autoimmune disease, which is jointly affected by humoral and cellular immunity. It has been more than 100 years since the discovery of HT. During this period, studies have reported the main clinical features of HT and the diagnostic criteria based on these features have been developed, such as ultrasonic diagnosis and humoral diagnosis. However, the external manifestations of HT patients have no obvious symptoms, which leads to diagnosis postpone, especially those with normal thyroid function. In addition, hyperthyroidism or hypothyroidism caused by HT may also be misdiagnosed. These factors affected the diagnosis and treatment of the disease to some extent. Therefore, more attention should be paid to external manifestations in the future. It would help doctors to make more accurate judgments and treatments in time. Moreover, patients with hyperthyroidism and hypothyroidism should be tested for TPO-Ab and TG-Ab to determine whether they have HT.

The pathogenic factors of HT are diverse. Except genes, imbalance of nutrient intake, negative emotions, and intestinal flora disorder, external factors (environmental pollution and virus infection) play an important role. However, many factors that have a definite correlation with HT are still controversial, and the influence of some factors on HT is still unknown. A clear understanding of the pathogenic factors is essential for prophylaxis and treatment of HT. Therefore, further research is still needed in this area, which is of great significance in clinical application.

The pathogenesis of HT is complex and involves many factors. The most intuitive one is the appearance of antigens and the increase of antibody titer, and further is the change of lymphocytes, such as T lymphocytes and NK cells. Many studies believe that the imbalance of T cells and their related cytokines, especially the change of Th1/Th2 and Th17/Treg ratio, is the main cause of HT. Other factors, such as oxidative stress, apoptosis, and changes in miRNA levels, are involved in the HT's occurrence and development to a certain extent. However, most of the current mechanisms are inferred by comparing the physiological and pathological differences between normal people and patients. No research can clarify the specific pathogenesis, and more targeted research is needed. At present, there is no way to thoroughly treat HT. Therefore, deepening the study on the pathogenesis of HT, finding effective prevention and treatment strategies and research targeted drugs, and solving the HT's clinical situation-- cure the symptoms, not the disease, is the direction of future research.

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